

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2004/011365

International filing date (day/month/year)
06.10.2004

Priority date (day/month/year)
08.10.2003

International Patent Classification (IPC) or both national classification and IPC
C07D213/79, A61K31/435, A61P19/00, A61P29/00

Applicant
GLAXO GROUP LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/EP2004/011365

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 8-10

because:

- ☒ the said international application, or the said claims Nos. 8-10 (method of treatment) relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-13
	No: Claims	
Inventive step (IS)	Yes: Claims	4
	No: Claims	1-3,5-13
Industrial applicability (IA)	Yes: Claims	1-7,11-13
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 8-10 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: US-A-5 811 459 (BREAU LT ET AL) 22 September 1998 (1998-09-22)
D2: WO 01/19814 A (MERCK FROSST CANADA & CO; LACOMBE, PATRICK;
LABELLE, MARC; RUE L, REJEA) 22 March 2001 (2001-03-22)

1. Novelty (Article 33(2) PCT):

1.1 D1 discloses compounds antagonizing the effects of PGE2 at the EP1 receptor. The compounds of D1 do not comprise a cyclohexene moiety.

D2 discloses compounds used in the treatment of prostaglandin mediated diseases. The compounds of D2 do not comprise a cyclohexene moiety.

1.2 Since the compounds of formula (I) are not known from the prior art the subject-matter of claims 1-13 can be considered novel.

2. Inventive Step (Article 33(3) PCT):

2.1 D1 can be seen as the closest prior art since it discloses structurally close compounds which antagonize the effects of PGE2 at the EP1 receptor.

The compounds of formula (I) structurally differ from the compounds of D1 in the presence of a cyclohexene unit linking a phenyl or pyridyl ring with an aryl or

heterocyclyl ring. The compounds of D1 in contrast comprise an alkylene linker linking a phenyl ring with an aryl or heteroaryl ring.

In the description is disclosed that the compounds of the present invention are selective for EP1 over EP3 (see p. 45 of the description).

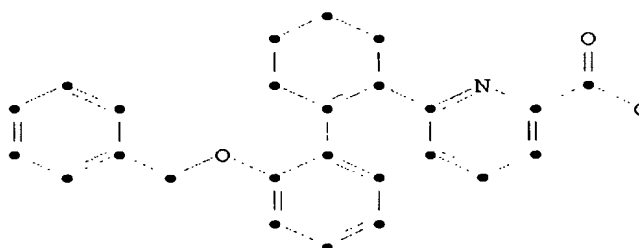
The technical problem then can be seen in providing compounds which are selective for EP1 over EP3.

- 2.2 The solution suggested by the Applicant are the compounds of formula (I). Such compounds are not obvious from D1 or a combination of D1 and D2.

However, it is doubtful that all compounds embraced by claim 1 solve said technical problem. Claim 1 embraces a huge number of compounds which have not been explored in the description as to their biological activity.

In contrast, all compounds which have been tested according to the description

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Having in mind that in the medicament field small structural changes often give rise to substantial and unexpected changes in activity and that the difference between D1 and the compound of formula (I) is smaller than the difference between the different compounds falling within the definition of formula (I), a generalization of experimental results for compounds with quite different structures does not appear to be justified.

It is therefore doubtful that all alternatives covered by the broad scope of the claims would achieve the desired technical effect.

An inventive step therefore can only be acknowledged for the subject-matter of

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The subject-matter of claims 1-3 and 5-13 cannot be considered inventive.

3. Industrial Applicability (Article 33(4) PCT):

3.1 The subject-matter of claims 1-7 and 11-13 is considered to be industrially applicable.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO03/084917	16/10/03	07/04/03	08/04/02

Re Item VII

Certain defects in the international application

The last paragraph of p. 45 of the description is considered unnecessary (Rule 9 (iv) PCT).